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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,515	EATON ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0406*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 04/10/2006 has been entered.

Claims 1–5 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC §§ 101, 112

Claims 1–5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants argue that Hu and LaBaer are not relevant because the instant application does not rely on microarray data. In this regard, applicants refer to Kuo (Exhibit 1, 04/10/2006). Applicants' arguments have been fully considered but they are not persuasive. From the evidence provided it cannot be ascertained if Kuo's microarray data was consistent or inconsistent with Kuo's RT-PCR data. Kuo's poor correlation between microarray and proteomic expression profiles does not speak to changes in mRNA attributable to disease-independent differences between samples. Therefore, applicants' reliance on Kuo is misplaced.

Applicants argue that there is no evidence of record that a skilled artisan would question the tumor-dependence of the differential expression of PRO874 mRNA in pooled samples. Applicants' arguments have been fully considered but they are not persuasive. Applicants'

comments regarding the accuracy of pooled samples are acknowledged. However, the utility of the PRO874 polypeptide lies in its ability to differentiate normal tissue from tumor tissue. The first Grimaldi declaration (Exhibit 1, 12/10/2004) states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. This statement is in contrast to the specification's teachings, which discloses:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. Page 140, paragraph 0350.

The declaration does not provide anything specific concerning PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in tumor tissue and normal tissue. It is unknown what level of difference is being reported or how many samples were tested. Hu and LaBaer are evidence that a skilled artisan would consider the precise level of PRO874 gene expression as relevant.

In practicing the invention some value for PRO874 polypeptide expression must be obtained in order to distinguish normal tissue from tumor tissue. Establishing a cutoff value for this distinction would be difficult unless one knows the typical degree of variation within the pool, which applicants have not provided. There is no evidence of record concerning the normal range in PRO874 mRNA levels or PRO874 polypeptide levels. There is no evidence of record that a normal range of PRO874 mRNA or PRO874 polypeptide levels could be defined that would distinguish normal tissue from tumor tissue. Without knowledge of the typical degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue. Pooled samples would also obscure the variation between

samples, making the disclosed results for PRO874 polynucleotide expression less useful, accurate and informative than if results from individual samples had been provided. In fact the range of values from normal and/or tumor tissue could be so broad that it would be impossible to distinguish normal tissue from tumor tissue.

Applicants argue that neither Hu nor LaBaer identify a threshold expression level necessary to establish diagnostic relevance. Applicants' arguments have been fully considered but they are not persuasive. A detection of a tumor-independent change in gene expression cannot be used as a diagnostic marker because it is tumor-independent.

Applicants argue that Haynes and Gygi are irrelevant to applicants' assertions. Applicants' arguments have been fully considered but they are not persuasive. It is noted that Applicants have not examined whether the reported change in PRO874 transcripts is correlated with a corresponding change in PRO874 polypeptide expression. It is further noted that Applicants' differential analysis is based upon comparing the steady-state levels of PRO transcripts in one or more normal tissues with the steady state levels of PRO transcripts in one or more tumor tissues. See the specification at page 140, paragraph 0530:

> Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor.

Applicants assume that PRO874 transcript levels are indicative PRO874 polypeptide levels. The specification fails to provide any testing of PRO874 polypeptide levels. Haynes teaches:

> "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis" (page 1863, right column, full paragraph 2).
>
> "The multi-level control of protein synthesis and degradation in cells means that only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts." Page 1870 left column, last full paragraph;

Because there are numerous levels of control of protein synthesis, degradation, processing and modification, which are only apparent by direct protein analysis the skilled artisan would not know if the disclosed change in PRO874 mRNA transcripts is associated with a corresponding change in the level of PRO874 protein. Hence, the skilled artisan would not know if or how PRO874 polypeptide expression would change in cancer. This conclusion is supported by Allman (Blood. 1996 Jun 15;87(12):5257-68), Molecular Biology of the Cell, 3rd ed. (Exhibit 1, 08/10/2005), Molecular Biology of the Cell, 4th ed. (Exhibit 4, 12/10/2004), Genes VI (Exhibit 3, 08/10/2005), the Polakis declaration (Exhibit 3, 12/10/2004), and Meric (Mol Cancer Ther. 2002 Sep;1(11):971-9) (Exhibit 5, 08/10/2005).

Applicants argue that Allman is not contrary to applicants' asserted utility and that Allman supports applicants' utility. Applicants' arguments have been fully considered but they are not persuasive. If one is to argue, as applicants have argued, that because PRO874 transcripts are differentially expressed in tumors it is more likely than not that the PRO874 polypeptide is differentially expressed in tumors, and therefore the PRO874 polypeptide and antibodies can be used for tumor diagnosis, then one must also accept the argument that because resting B cells and germinal center B cells express similar BCL-6 mRNA levels it is more likely than not that the BCL-6 protein is not differentially expressed in these two cell populations, and

therefore the BCL-6 protein and antibodies thereto cannot be used as a marker for germinal center B cells. One must also accept the argument that because germinal center B-cells express dramatically more BCL-6 protein than resting B cells it is more likely than not that BCL-6 mRNA is differentially expressed in these two cell populations, and therefore BCL-6 mRNA can be used as a marker for germinal center B-cells. Allman indicates that this is not so, and therefore Allman does not support applicants' position. The fact that it was unexpected that increases in BCL-6 protein were not correlated with a corresponding change in the level of BCL-6 mRNA only establishes that the skilled artisan would not know if or how PRO874 polypeptide expression changes in tumors. To argue that Allman supports applicants' position because Allman did not obtain the anticipated results is akin to arguing that the skilled artisan could experiment with PRO874 mRNA and polypeptide levels and determine for themselves how to use the claimed invention. Unlike Allman, Applicants have not provided any testing of the role, activity or expression of the PRO874 polypeptide.

The examiner relied on the following statements in Chen (Mol Cell Proteomics. 2002 Apr;1(4):304-13):

> "The use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of a protein present in a given cell or tissue." Page 304, right column, full paragraph.
>
> "Correlation analyses showed that protein abundance is likely a reflection of the transcription for a subset of proteins, but translation and post-translational modifications also appear to influence the expression levels of many individual proteins in lung adenocarcinomas." Paragraph bridging pages 304 and 306.

Applicants' arguments are directed to the statement in Chen that "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer

samples" (sentence bridging pages 311-312). However, this global analysis of the relationship between mRNA and protein abundance was in addition to and distinct from Chen's correlation a mRNA/protein abundance in the tumor samples, and the examiner did not rely on this global analysis.

Applicants argue that argue that "Chen merely selects proteins whose identity could be determined regardless of any changes in expression level" (underlining omitted), citing page 306, right column. Applicants argue that it is not known if the genes were differentially expressed. Applicants argue that Chen did not distinguish between cancer and normal samples. Applicants argue that the lack of correlation reported by Chen could be the result of a lack of substantial changes in mRNA. Applicants argue that Chen did not select samples that showed a difference in mRNA expression level. Applicants' arguments have been fully considered but they are not persuasive. According to applicants' exhibits, arguments, declarations, and asserted dogma changes in the level of an mRNA are associated with a corresponding change in the level of the encoded polypeptide. Therefore, according to applicants' exhibits, arguments, declarations, and asserted dogma, a change in the level of an mRNA should be correlated with a corresponding change in the level of the encoded protein regardless of the type of sample, i.e., regardless of whether the change was observed between two tumor samples or between a tumor sample and a normal sample. Chen statistically analyzed mRNA and protein levels (paragraph bridging pages 306 and 308). Spearman correlation coefficients of the proteins and their associated mRNA for each protein spot were generated using all 76 lung adenocarcinomas and nine non-neoplastic lung tissues (paragraph bridging pages 308-309). Figures 2A-C clearly show that for different samples a discerned change in the level of mRNA is not always associated with a corresponding

change in the level of protein and that similar mRNA levels do not correlate with similar protein levels. Applicants reference to Celis is acknowledged. However, according to Chen, Celis used proteomics and microarray analysis, which applicants have disparaged as inaccurate. Apparently, when proteomics and microarray analysis supports applicants' position it is accurate, and when it does not it is inaccurate. See applicants' arguments regarding Hu, LaBaer, Hancock, and Gygi. Furthermore, there is no evidence of regard that the PRO874 polypeptide is either abundantly expressed or abundantly under-expressed.

Applicants argue that Hancock is attributing the incongruities between expression profiling and proteomics to shortcomings in proteomics methods, and not to actual, accurately measured protein and mRNA levels in cells. Applicant's arguments have been fully considered but they are not persuasive. Regarding the shortcomings of proteomic methods, Hancock is speaking of the push to validate currently available biomarkers in an extensive clinical setting:

> The Editor has become aware of a recent push to validate currently available biomarkers in an extensive clinical setting. ... The challenge in this situation is to balance the need of patients for better, early diagnosis of disease with the need to have high-quality markers for the expensive and time-consuming validation process. This Editor believes that proteomics is at too early a stage for this new technology to have generated a quality list of markers.

Applicants' augments regarding the alleged shortcomings in proteomics are just as equally applicable, if not more so, to Applicants' asserted diagnostic utility given the specification's paucity of information regarding PRO874 gene expression and the total lack of information concerning PRO874 polypeptide expression. There is no evidence of record that PRO874 transcripts were measured accurately or that the changes seen were consistent and reproducible. The skilled artisan would not know if the changes seen were disease-dependent or disease-independent. The examiner does not agree that Hancock is attributing the incongruities between

expression profiling and proteomics to shortcomings in proteomics methods, and not to actual, accurately measured protein and mRNA levels in cells. Hancock does not make such a statement or implication. Hancock states:

> With the advent of genomics and, later, proteomics, there has been a substantial investment in using these new tools to generate additional biomarkers. The problem with this new information is that it is too early to get consensus on what is a useful marker or what is a good patient population for such a study. Therefore, it is unclear whether the new markers currently in hand will give better clinical information than the ones that have been used in the past. An additional problem is that the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling.

Hancock indicates that an additional problem with using genomics and proteomics to generate additional biomarkers is that the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling, which is consistent with the examiner's finding that a skilled artisan would not know if, or how, PRO874 expression would change in tumors.

Applicants submit a total of 113 references (Exhibits 1-23, 04/10/2006). Exhibits 1-23 (04/10/2006) have been considered. However, none of this evidence discloses anything specific regarding PRO874 mRNA expression, PRO874 polypeptide expression, or the correlation between the two in normal tissue and tumor tissue. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO874 transcripts and PRO874 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, as evidenced by the Polakis declaration (Exhibit 3, 12/10/2004). Regarding Orntoft (Mol Cell Proteomics. 2002 Jan;1(1):37-

45; and, Exhibit 2, 04/10/2006) and Futcher (Exhibit 13, 04/10/2006), there is no evidence of record that PRO874 mRNA or protein is either abundantly expressed or abundantly under-expressed. Orntoft notes that it was only possible to compare mRNA and protein alterations in relatively few cases of well focused abundant proteins (Abstract) and that in the few cases analyzed, mRNA and protein levels showed a striking correspondence although in some cases we found discrepancies that may be attributed to translational regulation, post-translational processing, protein degradation, or a combination of these (page 44, right column, full paragraph 2) and that it is at present unknown whether DNA copy number is one of the mechanisms behind alteration of these eleven proteins where they found a significant correlation between DNA copy number, mRNA expression, and protein level (page 45, left column, full paragraph 1). Furthermore, Orntoft clearly suggest that both transcript and protein levels need to be analyzed (page 45, left column, full paragraph 2). Unlike Orntoft, Applicants have not provided any testing of PRO874 polypeptide expression. Hu and LaBaer caution researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Plus, there is no evidence of record that either PRO874 mRNA or PRO874 polypeptide is abundantly expressed in either tumor tissue or normal tissue. Orntoft does not provide any information regarding PRO874 mRNA expression, PRO874 polypeptide expression or the correlation between the two in tumor tissue and normal tissue. Thus, considered as a whole the evidence supports and is consistent with the examiner's position that the skilled artisan would not know if or how PRO874 polypeptide expression changes in cancer and that the present application fails to disclose to disclose enough information about the invention to make its usefulness immediately apparent to those familiar with the technological field of the

invention. In addition, Orntoft used gene expression and profiling techniques (microarrays and proteomics) (page 37, right column, last full paragraph) that Applicants have disparaged as inaccurate.

Applicants are not being asked to prove the asserted diagnostic utility either as a matter of statistical certainty or beyond a reasonable doubt. Rather, the facts to be established are, is the reported change in PRO874 transcripts tumor-dependent or tumor-independent and, if the reported change is tumor-dependent, is there a corresponding change in PRO874 polypeptide expression. The specification does not establish if the disclosed change in PRO874 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Applicants have not provided any testing of PRO874 polypeptide expression. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO874 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO874 polypeptide, the specification does not provide some immediate benefit to the public for the PRO874 polypeptide and claimed antibodies thereto. The correlation between the disclosed change in PRO874 mRNA and a change in PRO874 polypeptide expression is unknown and is not disclosed.

The specification does not make any specific assertion regarding positive correlations between PRO874 mRNA expression and PRO874 polypeptide expression, i.e., if PRO874 mRNA is up-regulated, PRO874 polypeptide is up-regulated or *vice versa*. Furthermore, The second Grimaldi declaration filed (Exhibit 2, 12/10/2004) asserts that:

> " ... even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others,

> then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy." Paragraph 6.

The Ashkenazi declaration filed (Exhibit 5, 12/10/2004) asserts that:

> "absence of gene product overexpression still provides significant information for cancer diagnosis and treatment." Paragraph 6.

Applicants are arguing that whatever the expression level and whatever the correlation, the PRO874 polypeptide is useful because skilled artisans could figure out for themselves what any observed experimental result might mean. The specification does not disclose anything regarding "more accurate tumor classification." The examiner does not agree that such a disclosure provides a "specific benefit in currently available form" because the expression of all polynucleotides or polypeptides from a tumor sample can invariably be classified as either increased, decreased, non-existent, or unchanged as compared to some standard level of expression. It can then be asserted that all proteins or polynucleotides that are expressed in this manner can be used to detect or characterize the tumor. Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific nor a substantial utility. Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Applicants have not provided any testing of the expression of the PRO874 polypeptide.

Applicants should provide substantial evidence of a diagnostic utility unless one of skill in art would accept such utility as obviously correct. There is no indication that a skilled artisan

would accept without question that the reported change in PRO874 transcripts is tumor-dependent or that the PRO874 polypeptide is differentially expressed in tumor tissue as compared to normal tissue in a manner consistent with the reported change in PRO874 transcripts. Neither the specification nor any of Applicants' arguments, exhibits, declarations or other evidence provide any specific data disclosing if or how PRO874 polypeptide expression changes in tumor tissue. Instead, Applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO874 transcripts and PRO874 polypeptide expression to argue that it is more likely than not that a change in PRO874 transcripts is correlated with an assumed change in PRO874 polypeptide expression. Without any evidence of the expression of PRO874 in tumor tissue this argument is of no avail to Applicants. Applicants' arguments, exhibits and declarations only show that it is not implausible that invention will work for its intended purpose. In view of the countervailing evidence, Applicants' arguments, exhibits and declarations are insufficient to meet the utility requirement because they are insubstantial evidence that expression of the PRO874 polypeptide changes in a manner that corresponds to the reported change in PRO874 transcripts.

Claims 1–5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Claim Rejections - 35 USC § 112

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support for the limitation "amino acids 34-321 of SEQ ID NO: 10" cannot be found in the disclosure as originally filed, which raises the issue of new matter. Applicants argue that support for this limitation can be found in paragraph 0196. Applicant's arguments have been fully considered but they are not persuasive. Paragraph 0196 discloses that it is conceivable and possible that other methionine residues located either upstream or downstream from the amino

acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides. However, the species methionine residue #34 as the starting amino acid is not supported by this generic disclosure because there is no express, implicit, or inherent support for this species to the exclusion of all the other species. In other words, there is no evidence of record that the disclosure would not reasonably lead the skilled artisan to this particular species.

Applicants argue that the examiner misstates the test for compliance with the written description requirement. Applicants submit that it would be apparent to any skilled artisan that the first methionine in SEQ ID NO: 10 is likely the start methionine. Applicants' arguments have been fully considered but they are not persuasive. The disclosure that it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides makes it clear that Applicants have not adequately described "amino acids 34-321 of SEQ ID NO: 10" because there is no evidence of record that amino acid #34 is employed as a start site. In the absence of any evidence that amino acid #34 is employed as a start site, the generic disclosure of what may be possible or conceivable does not convey with reasonable clarity to those skilled in the art that Applicants were in possession of the invention as now claimed.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under

37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
JUNE 25, 2006